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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/961,086	09/21/2001	Douglas D. Ross	A9118	6592

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EXAMINER	
UNGAR, SUSAN NMN	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 10/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/961,086	ROSS ET AL.	
	Examiner	Art Unit	
	Susan Ungar	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *26 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *5-7 and 38-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) *39-40* is/are allowed.

6)☐ Claim(s) *2-5 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/8/06*; 8/15/06
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submissions filed on May 8, 2006 are acknowledged and have been entered. Claims 38-40 have been added. Claims 39-40 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions. An action on the RCE follows.

2 Claims 5-7 and 38 are pending and currently under examination.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4, The following rejections are being maintained:

Claim Rejections - 35 USC 103

5. Claims 5-7 remain rejected and claim 38 is rejected under 35 USC 103 for the reasons previously set forth in the paper mailed November 8, 2006, Section 4, pages 2-7.

It is noted that the limitation "pharmaceutical composition" recited in newly added claim 38 is view as a recitation of intended use and therefore is not given weight in comparing the claim with the prior art. Claim 38 reads on the product *per se*, which is an isolated antibody that binds to SEQ ID NO:1.

Applicant argues that no evidence has been presented that the particular species of antibodies recited in the pending claims would be included in the genus of antibodies that would result from the use of Purnelle or Kirby as immunogens. The argument has been considered but has not been found persuasive because,

given the identity of the numerous stretches of amino acids in common or conservatively substituted, anyone of ordinary skill in the art would believe it more likely than not that antibodies to the polypeptides of Purnelle or Kirby would also bind to the instantly claimed SEQ ID NO:1. Further, although the references do not specifically recite that antibodies to the disclosed polypeptides would cross-react, that is bind to SEQ ID NO:1, the claimed antibodies appear to be the same as the antibodies of the combined prior art references, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the combined prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from that taught by the combined prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Applicant argues that given the teaching of Herbert that the three-dimensional structure of the epitope is essential for antibody binding, the skilled artisan would not expect that two polypeptides having only 30.5% and 32.1% identity to SEQ ID NO:1 would form identical antigenic determinants in the native folding of the proteins as those found in the polypeptide of SEQ ID NO:1. The argument has been considered but has not been found persuasive because Applicant is arguing limitations not recited n the claims as currently constituted. Nothing in the claims requires that the antibodies bind to the native conformation. In point of fact, antibodies that bind to the denatured form of a protein, for use, for example in Western blotting, are conventional in the art.

Applicant argues that the skilled artisan would not expect antibodies raised against either the Purnelle or Kirby polypeptide to be cross-reactive with the polypeptide of SEQ ID NO:1 and points to the submitted Ross Declaration. In particular, Dr. Ross Declares, in agreement with Examiner, states that the polypeptides of both Purnelle and Kirby have multiple regions of five or more amino acids with 100% identity to contiguous amino acids of SEQ ID NO:1. Dr. Ross specifically identifies three regions of five or more identical amino acids between SEQ ID NO:1 and the polypeptide of Purnelle et al and four regions of five or more identical amino acids between SEQ ID NO:1 and the polypeptide of Kirby. It is here noted that Dr. Ross argues that there is no evidence that any of the shared conservative amino acids of the polypeptides would be required to form specific tertiary structures that would contribute to the three dimensional structure of the protein and thus has apparently dismissed the many regions that encompass conserved amino acids that include 5 or more amino acids that would be expected to stimulate antibodies that would cross react with SEQ ID NO:1. In particular, In addition to the three regions in Purnelle identified by Dr. Ross in the Purnelle reference, Examiner has identified seven additional regions which include conservative substitutions and specifically notes that one of the regions identified by Dr. Ross as having a total of 7 identical contiguous amino acids with SEQ ID NO:1, in point of fact when conservative substitutions are included, has a stretch of 14 amino acids contiguous amino acids. Further, a review of the identity between Kirby et al and SEQ ID NO:1 also reveals seven additional regions which include conservative substitutions. Although there is no evidence that the amino acids comprising shared conservative amino acids would in fact produce antibodies to SEQ ID NO:1, given the teachings previously set forth, although the combined

references do not specifically teach that the known prior art polypeptides would produce antibodies that bind with SEQ ID NO:1, the claimed antibodies appear to be the same as the antibodies of the combined prior art references, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the combined prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from that taught by the combined prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Dr. Ross further argues that there are "no large regions of homology between the polypeptides of Kirby or Purnelle et al and SEQ ID NO:1 and opines that (1) "the three dimensional conformation that would be adopted upon folding of the three polypeptides would not be expected to result in any antigenic determinants in common between the three polypeptides and given that there is no evidence of shared antigenic determinants, there would be no reasonable expectation that an antibody raised against either the Purnelle et al or the Kirby et al would be cross-reactive with and bind to the polypeptide of SEQ ID NO:1, (2) antibodies can be generated that recognize discreet, contiguous portions of a polypeptide. However, Applicant further argues that such regions of the polypeptide must be exposed on the surface of the polypeptide and they must be antigenic. There is no indication in the documents cited by Examiner that any of the identical regions of.r either Kirby or Purnelle are exposed on the surface of the polypeptides. Further, there is no evidence that the regions of identity in the

polypeptide of SEQ ID NO:1 are exposed on the surface of the polypeptide, (3) antigenicity plots were generated and it was found that none of the regions appears to be highly antigenic and because the plots found that they were not highly antigenic, none of them would be expected to serve as antigenic determinants, thus there is no reasonable expectation that the antibodies generated against regions of 100% identity in either Purnelle et al or Kirby et al would in fact bind to SEQ ID NO:1.

The opinions have been considered but has not been found persuasive given that (1') cross reactivity of antibodies is a well known phenomenon and does not require that "large areas" of a protein be homologous in order to make cross-reacting antibodies, (1') (2') Applicant is arguing limitations not recited in the claims as currently constituted. Nothing in the claims requires that the antibodies bind to the native conformation. In point of fact, antibodies that bind to the denatured form of a protein, for use for example in Western blotting, are conventional in the art, (3') Dr. Ross does not state that the identical portions are not immunogenic, only that they are not highly antigenic. Further, Examiner never suggested that antibodies would be generated only against regions of 100% identity. Given the teachings previously set forth, although the combined references do not specifically teach that the known prior art polypeptides would produce antibodies that bind with SEQ ID NO:1, the claimed antibodies appear to be the same as the antibodies of the combined prior art references, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the combined prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to

the contrary, the burden is on the applicant to prove that the claimed product is different from that taught by the combined prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Applicant argues that the antibodies recited in claim 1 comprise a small number of species of the large genus of antibodies that might arise from the production of antibodies using fragments of the polypeptides of Purnelle and Kirby. The argument has been considered but has not been found persuasive since Examiner never suggested using fragments of the polypeptides of Purnelle and Kirby to produce antibodies.

Applicant reiterates arguments drawn to motivation to select specific antibodies. The argument has previously been considered and has not been found persuasive for the reasons of record. Further, the claims are not drawn to antibodies that are specific to SEQ ID NO:1, rather the claims are drawn to antibodies that bind to SEQ ID NO:1.

Applicant reiterates arguments drawn to no suggestion or motivation to make the claimed invention. The arguments have been previously considered but have not been found persuasive for the reasons of record.

Applicant argues that antibodies to native proteins would not be expected to cross react. The argument has been considered but has not been found persuasive for the reasons set forth previously and above, that is, Applicant is arguing limitations not recited in the claims as currently constituted. Nothing in the claims requires that the antibodies bind to native protein.

The arguments and Declaration have been carefully considered but have not been found persuasive and the rejection is maintained. It is noted that objective

evidence showing that polyclonal antibodies to the Purnelle and Kirby polypeptides do not cross-react with SEQ ID NO:1 would obviate the instant rejection.

New Grounds of Rejection

Claim Rejections - 35 USC 112

6. Claim 38 is rejected under 35 USC 112, first paragraph because the specification, while enabling for a composition comprising antibody that binds to SEQ ID NO:1 does not reasonably provide enablement for a pharmaceutical composition comprising an isolated antibody that binds to SEQ ID NO:1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to a pharmaceutical composition comprising an isolated antibody that binds to SEQ ID NO:1. Inherent in the recitation of a pharmaceutical composition is the *in vivo* use thereof for the treatment of disease. This means that the claims are drawn to a composition to be used for the *in vivo* treatment of disease.

The specification teaches that the discovery of the Breast Cancer Resistance Protein, BCRP (SEQ ID NO:1) greatly advances the knowledge in the art of the drug resistance mechanism by providing a novel xenobiotic transporter which is overexpressed in a variety of drug-resistant human cell lines, and confers resistance to many chemotherapeutic agents (p. 3, para 1). It is an object of the invention to provide antibodies to BCRP. It is also an object of the invention to provide a method of reversing the drug resistance of cancer cells by administering BCRP antibodies/a method of enhancing a patient's chemotherapy treatment for

breast cancer by administering antibodies to the patient to inhibit BCRP (p. 4). Thus it appears that the intended use of the claimed pharmaceutical composition is drawn only to the treatment of multidrug resistant cancers.

The specification exemplifies *in vitro* studies drawn to the effects of chemotherapeutic drugs on BCRP-transfected MCF-7 cells, Example 10, wherein it was found that BCRP-transfected cells were more resistant to chemotherapeutic drugs than non-transfected cells. The specification exemplifies *in vitro* studies drawn to the effects of FTC on BCRP transfected MCF-7 cells, Example 14, as well as the expression of BCRP in blast cells from patients with AML as detected by RT-PCR (Example 11).

One cannot extrapolate the teaching of the specification to the scope of the claim because it appears that the only intended use disclosed in the specification for the pharmaceutical composition is the *in vivo* use of the composition for the treatment of multidrug resistance in cancer. However, the art recognizes the unpredictability of the cancer therapy arts. Although drawn to a broad range of anti-cancer therapeutics, the teachings of Gura (Science, 1997, 278:1041-1042) are relevant to the instant rejection. Gura teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Because of the known unpredictability of the art, in the absence of any objective evidence that the pharmaceutical composition could be used to treat cancer as contemplated in the specification, no one skilled in the art would accept the assertion that the claimed pharmaceutical composition would

function as claimed based only upon the statement, as set forth above that "it is also an object of the invention to provide a method of reversing the drug resistance of cancer cells by administering BCRP antibodies/a method of enhancing a patient's chemotherapy treatment for breast cancer by administering antibodies to the patient to inhibit BCRP"

It is noted that MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

Given the unpredictability of the art, given the lack of any objective evidence that the pharmaceutical composition would function as claimed, given the lack of adequate disclosure in the specification, given that little is known in the art about the claimed invention, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

7. No claims allowed.

8. All other objections and rejections recited in the previous Office Action are hereby withdrawn.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (571) 272-0837. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at 571-272-0787. The fax phone number for this Art Unit is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Susan Ungar
Primary Patent Examiner
September 21, 2006